REVISED

U.S. EPA HIGH PRODUCTION VOLUME CHEMICAL VOLUNTARY TESTING PROGRAM

TEST PLAN

2-ETHYLHEXYL DIPHENYL PHOSPHATE

Submitted by:

FERRO CORPORATION
CLEVELAND, OHIO

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INTRODUCTION

2-Ethylhexyl diphenyl phosphate, CAS Registry Number 1241-94-7, is a general purpose plasticizer for most commercial resins including polyvinyl chloride and its copolymers, cellulose nitrate, cellulose acetate-butyrate, ethyl cellulose, polymethyl methacrylate and polystyrene. 2-Ethylhexyl diphenyl phosphate (EDP) is approved for indirect food contact. EDP is a clear, odorless liquid. The chemical structure, formula and identification numbers for 2-Ethylhexyl diphenyl phosphate are given below:

CAS No: 1241-94-7
EINECS No: 214-987-2
EINECS Name: 2-Ethylhexyl diphenyl phosphate
Molecular formula: $C_{20}H_{27}O_4P$
Molecular weight: 362.4 g/mole
Structural formula:

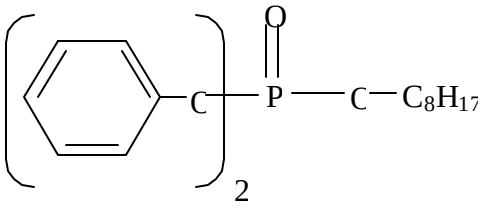

Table 1
CHEMICAL-PHYSICAL PROPERTIES
OF 2-ETHYLHEXYL DIPHENYL PHOSPHATE

Property	**Value**
Melting point	-54°C (pour point)
Boiling point (at 13.33 hPa)	239°C
Relative density	1.07-1.09 at 20°C
Vapour pressure	$6.29X10^{-5}$ mmHg @ 25°C
Water solubility	0.38 mg/l at 22°C
Octanol-water partition coefficient (log value)	5.73 @ 25°C
Henry's law constant	0.065 Pa m^3/mole at 20°C or 0.12 Pa m^3/mole at 25°C
Flash point	224°C
Autoignition temperature	>500°C
Explosivity	No data available

TEST PLAN RATIONALE

Ferro Corporation is committed to providing EPA with reliable data necessary to complete the SIDS screening matrix for the HPV voluntary challenge; however, Ferro Corporation is also committed to judicious use of research animal resources. As pointed out in its 2002 submission to EPA, Ferro Corporation committed to obtaining adequate documentation on existing studies of 2-ethylhexyl diphenyl phosphate in order to utilize these studies in the toxicology profile for 2-ethylhexyl diphenyl phosphate. Documentation has become available to Ferro, and the HPV Test Plan originally submitted has been revised to reflect reliance on existing studies.

Specifically, information has become available on the environmental effects, ecotoxicity and health effects of 2-ethylhexyl diphenyl phosphate since the initial filing of this test plan. The information is in the form of toxicity and other testing reports, and is judged to be reliable[1]. Accordingly, Ferro is revising its HPV Test Plan for 2-Ethylhexyl diphenyl phosphate and presents this revised plan in Table 2.

2-Ethylhexyl diphenyl phosphate is of low acute mammalian toxicity. Acute oral LD50 values for 2-Ethylhexyl diphenyl phosphate are well above current limit test values for this endpoint, i.e., > 10 mg/kg, meaning 2-Ethylhexyl diphenyl phosphate would be considered "practically non-toxic" if it were a consumer product, which it is not. Human skin testing has established that 2-Ethylhexyl diphenyl phosphate is slightly to the eyes and skin but is not a skin sensitizer. Repeat-dose oral testing in rodents has established that 2-Ethylhexyl diphenyl phosphate affects target organs (the liver and adrenals) only at daily dietary doses greater than 150mg/kg/day. Reproductive function (in rodents) is not disturbed until these daily doses are exceeded, in other words, until parental systemic toxicity is produced.

2-Ethylhexyl diphenyl phosphate is not genotoxic in bacterial, yeast or mammalian cells when tested with and without standard protocols employing exogenous metabolic activation systems. *In vivo* testing failed to show evidence of chromosome damage in rodent bone arrow cells.

The environmental toxicity of 2-Ethylhexyl diphenyl phosphate has been described for effects in Daphnia, algae and rainbow trout. Both acute effects (algae) and chronic effects (Daphnia and trout) have been reported, as well as aquatic and sediment fate and photolysis values.

Taken together, these data adequately provide testing results for the base set of environmental and human health effects endpoints identified by EPA in the HPA SIDS Level 1 data development screen. Accordingly, no additional effects testing is proposed

[1] Reliable according to the standards specified by Klimisch, et al., (Regulatory Toxicology and Pharmacology, 25, 1-5, 1997) or the EPA High Production Volume Challenge Program Guidelines For Determining the Adequacy of Existing Data Bases (http://www.epa.gov/chemrtk/datadfin/htm).

for 2-Ethylhexyl diphenyl phosphate. Hydrolysis testing is planned for 2-Ethylhexyl diphenyl phenol phosphate.

TEST PLAN: 2-ETHYLHEXYL DIPHENYL PHOSPHATE

Table 2 lists the HPV testing planned by Ferro Corporation for 2-ethylhexyl diphenyl phosphate. The one test is:

Hydrolysis Testing OECD Test Method 111

CONCLUSION

2-Ethylhexyl diphenyl phenol sold or distributed in the U.S. by Ferro is of uniform composition. The material is used as an intermediate in chemical processing, principally of plastics. Existing test results, although dated in some cases, are reliable and entirely applicable to current assessments of 2-Ethylhexyl diphenyl phenol. New testing would violate animal use goals without producing additional meaningful scientific information, and would thus also be unnecessarily burdensome.

With the exception of hydrolysis testing, Ferro proposes no additional testing of 2-Ethylhexyl diphenyl phoshphate. Existing studies, summarized in Appendix 1 account for the data requirements identified by EPA in the HPV voluntary data development program.

Table 2 2-ETHYLHEXYL DIPHENYL PHOSPHATE HPV TEST PLAN

HPV DATA ENDPOINT	ENDPOINT VALUE	PROPOSED DATA DEVELOPMENT
1. CHEMISTRY		
Melting Point	-54ºC (pour point)	No testing proposed
Boiling Point	239ºC @ 13.33 hPa	No testing proposed
Vapor Pressure	$6.29X10^{-5}$ mmHg @ 25ºC	No testing necessary
Water Solubility	0.38 mg/l @ 22ºC	No testing proposed
Partition Co-Efficient	5.73 @ 25ºC	No testing proposed
2. ENVIRON-MENTAL FATE		
Photodegradation	$T_{1/2}$ = 20-166 days	No testing proposed
Hydrolysis (Stability in Water)	Data not Available	OECD Test Guideline 111
Biodegradation	Readily biodegradable 82% degraded after 28 days	No testing proposed
Fugacity –four compartment level III model	% in air = 0.071 % in soil = 74.8 % in water = 2.53 % in sediment = 22.6	No additional modeling proposed
3. HEALTH EFFECTS		
Acute Toxicity	LD50 > 24g/Kg	No testing proposed
Repeat Dose Toxicity	90 day oral dietary study in rats NOAEL <0.2% (~160mg/kg/day)	No testing proposed
Repro-Develop. Toxicity	One generation oral dietary study in rats REPRO NOAEL = 0.2% (~144mg/kg/day)	No testing proposed
Genetic Toxicity		
Bacterial mutation Test	Negative with and without activation	No testing proposed
Mammalian chromosome damage test	Negative with and without activation	No testing proposed
4. ECOTOXICITY		
Fish	LC50 > 0.38 mg/l	No testing proposed
Daphnia	EC50 = 0.12 – 0.18 mg/l	No testing proposed
Algae	EC50 = 0.2 mg/l for cell	No testing proposed

	survival	

APPENDIX 1

ROBUST SUMMARIES

2-ETHYLHEXYL DIPHENYL PHOSPHATE
CAS Number 1241-94-7

I. PHYSICAL-CHEMICAL ELEMENTS

Type: Melting Point
Value: -54°C
Decomposition: No
Sublimation: No
Method: Pour Point
Year: 2002
GLP: Unknown
Remarks: None
Quality : Not stated
Reliability: Reliable with restrictions
Reference: Ferro Corporation Technical Data Sheet No. 2311540C

Test Material: 2-ETHYLHEXYL DIPHENYL PHOSPHATE
Type Boiling Point
Value : 239°C
Decomposition : Yes
Sublimation : No
Method : Unknown
Year: Unknown
GLP: Unknown
Remarks: Determination at 13.33hPa (10mmHg)
Quality : Not stated
Reliability: Reliable with restrictions
Reference: Ferro Corporation Technical Data Sheet No. 2311540C

Test Material: 2-ETHYLHEXYL DIPHENYL PHOSPHATE
Type: Vapor Pressure
Value: $6.29X10^{-5}$ mmHg @ 25°C
Method: Unknown
GLP: Unknown
Year: Unknown

Remarks: None
Quality: Not stated
Reliability: Reliable with restrictions
Muir, D., et al., Environ Tox Chem, 4: 663-75, 1985

Test Material: 2-ETHYLHEXYL DIPHENYL PHOSPHATE
Type: Partition Coefficient
Value: Log Kow = 5.73
Method: Unknown
GLP: Unknown
Year: Unknown
Remarks: None
Quality: Unknown
Reliability: Reliable with restrictions
Saeger, VW., et al, Environ Science Technol. 13: 840-844, 1979

Test Material: 2-ETHYLHEXYL DIPHENYL PHOSPHATE
Type: Water solubility
Value: 0.38mg/L @ 22ºC
Method: Unknown
GLP: Unknown
Year: 1990
Remarks: None
Quality: Unknown
Reliability: Reliable with restrictions
Source: Monsanto Technical Report MO-90-9520

II. ENVIRONMENTAL FATE AND ECOTOXICITY

Test Material: 2-ETHYLHEXYL DIPHENYL PHOSPHATE (S-141, Lot Number Q11411)
Study type: Photolysis
Test concentrations: 1 mg/L
Test system: River water and purified water exposure in sunlight
Observations: Direct photolysis (in Milli-Q water); Non-photolytic degradation (in Milli-Q water); Direct/sensitized photolysis (in filtered river water); non-photolytic degradation (in filtered river water)
Results: At 1 mg/L (ppm), half-lives ranging from 20 to 166 days were observed with no evidence of significant direct or sensitized photolysis or chemical transformation.

The study director attributed the observed half-lives to artifact.
Statistical analysis of study data: Yes
Reliability: Reliable with restrictions
GLP: No, study data and report were subject to QA review
Reference: Monsanto Industrial Chemicals Company Environmental Sciences Section, Sunlight photolysis screening of Santicizer S-141, Report ES-81-SS-37, St. Louis, Mo.

Test Material: 2-ETHYLHEXYL DIPHENYL PHOSPHATE
Study type: Aerobic biodegradation OECD Guideline 301B; Ready Biodegradability
Test concentrations: 20 mg/L
Test system: Activated sludge;
Duration of study: 28 days
Observations: Not provided
Study endpoint: CO_2 evolution
Results: 82% degraded after 28 days
Statistical analysis of study data: Not stated
Reliability: Reliable with restrictions
GLP: No
Reference: J. American Oil Chemists Society 50: 159, 1973

Test Material: 2-ETHYLHEXYL DIPHENYL PHOSPHATE (S-141, Lot Number Q11411)
Study type: Biodegradation
Test concentrations: 1 mg/L
Test system: ^{14}C-labeled test material was incubated in lake water sediment (core chamber microcosm) and, separately, in lake water (10 gallon aquaria), for evaluation of degradation to CO_2. The sediment microcosm (duplicate 10 gal. aquaria) were established and stabilized for 18 months prior to initiation of testing.
Duration of study: 31 days
Observations: Direct photolysis (in Milli-Q water); Non-photolytic degradation (in Milli-Q water); Direct/sensitized photolysis (in filtered river water); non-photolytic degradation (in filtered river water)
Study endpoint: CO_2 evolution
Results: Lake water removal half-life = 4.9 days @ 500 microgram/L; lower CO2 production was observed for the sediment microcosm samples. ^{14}C-activity in the sediment at the conclusion of the stud ranged from 28-90%.
Statistical analysis of study data: Yes
Reliability: Reliable with restrictions
GLP: No, study data and report were subject to QA review
Reference: Monsanto Industrial Chemicals Company Environmental Sciences Section, The environmental fate of Santicizer S-141 in a lake water sediment microcosm study. Report ES-81-SS-86, St. Louis, Mo., December , 1982

Test Material: 2-ETHYLHEXYL DIPHENYL PHOSPHATE (S-141, BN-79-1384348-1d, Monsanto company)
Study type: Acute toxicity
Strain: Selenastrum capricornutum (green algae)
Test concentrations: triplicate cultures tested at 5 concentrations: 1.0, 0.6, 0.3, 0.1 and 0.06 mg/L
Controls: Medium (negative) and positive control
Duration of test material exposure: 96 hours
Study endpoint: 50% decrease in cellular chlorophyll , and 50% decrease in cell number at 96 hours
Observations: cell number, chlorophyll concentration, pH of growth culture medium,
Results: 96 hour EC50 for cell survival was 0.2 mg/L with 95% CI of 0.07-0.88;
96 hour EC50 for chlorophyll concentration was 0.2 mg/l
with 95% CI = 0.06-0.9
Statistical analysis of study data: Yes
Reliability: Reliable with restrictions
GLP: No
Reference: EG&G Bionomics Marine Research Laboratory, Report Number BP-79-4-54, April 1979,
Toxicity of S-141 (BN-79-1384348-1d) to the fresh water alga Selanastrum capricornicum.

Test Material: 2-ETHYLHEXYL DIPHENYL PHOSPHATE (S-141, BN-79-1384348-2)
Study type: acute toxicity
Strain: Daphnia magna
Test concentrations: quadruplicate cultures tested at 7 nominal concentrations: 0.28, 0.17, 0.10, 0.064, 0.036, 0.022 and 0.014mg/L.
15 Daphnia were placed in each aquarium.
Controls: Medium (negative) and positive control
Duration of test material exposure: 48 hours
Exposure apparatus: 2.0L glass aquaria with static exposure
Study endpoint: Survival
Observations: dissolved oxygen, temperature, hardness, alkalinity, pH, conductance
Statistical analysis of study data: Yes
48 hour LC50 = : 150 microgram/L (120-180 microgram/L 95%CI)
Reliability: Reliable with restrictions
GLP: No
Reference: EG&G Bionomics Aquatic Toxicology Research Laboratory, Report Number BW-79-9-537, The chronic toxicity of S-141 (BN-79-1384348-2) to the water flea (Daphnia magna). Wareham, MA., October, 1979.

Test Material: 2-ETHYLHEXYL DIPHENYL PHOSPHATE (S-141)
Study type: Acute toxicity
Strain: Paratanytarsus parathenogenetica (midge)
Test concentrations: triplicate cultures tested at 3 concentrations: 6.0, 1..5 and 0.38 mg/L
Controls: Medium (negative) and solvent (DMSO) control
Duration of test material exposure: 48 hours
Study endpoint: 50% decrease in cell number at 48 hours
Observations: cell survival, dissolved oxygen, pH of growth culture medium, water hardness, temperature
Results: 48 hour LC50 for cell survival was 0.50mg/L with 95% CI of 0.45-56;
Statistical analysis of study data: Yes
Reliability: Reliable with restrictions
GLP: No, study data and report were subject to QA review
Reference: Monsanto Industrial Chemicals Company Environmental Sciences Section, Acute toxicity of Santicizer S-141 to the midge, Paratanytarsus parathenogenetica, Report ES-81-SS-5, St. Louis, Mo.

Test Material: 2-ETHYLHEXYL DIPHENYL PHOSPHATE (S-141)
Study type: Acute toxicity, static exposure
Strain: Chironomus tentans (aquatic invertebrate)
Test concentrations: ten separate cultures, each tested at 5 concentrations: 2, 1, 0.5, 0.25 and 0.125 mg/L
Controls: Medium (negative) and solvent (DMSO) control
Duration of test material exposure: 48 hours, no aeration of aquaria
Study endpoint: 50% decrease in cell number at 48 hours
Observations: cell survival, dissolved oxygen, pH of growth culture medium, water hardness, temperature
Results: 48 hour LC50 for cell survival was 0.67mg/L (0.49-0.84);
Statistical analysis of study data: Yes
Reliability: Reliable
GLP: Yes
Reference: Monsanto Industrial Chemicals Company Environmental Sciences Section, Acute toxicity of Santicizer S-141 to Chironomus tentans, Report ES-82-SS-5, St. Louis, Mo., May, 1982.

Test Material: 2-ETHYLHEXYL DIPHENYL PHOSPHATE
Study type: Acute toxicity
Strain: Oncorhychus mykiss

Test concentrations: 96 hours static exposures
Duration of test material exposure: 96 hours
Study endpoint: Survival
Results: LC50 = > 0.38 mg/L (solubility limit of test material in water)
Statistical analysis of study data: Not stated
Reliability: Reliable with restrictions
Year: 1984
GLP: Yes
Reference: Monsanto Industrial Chemicals Company Environmental Sciences Section,), Report AB 79-0101A, St. Louis, Mo.

Test Material: 2-ETHYLHEXYL DIPHENYL PHOSPHATE (S-141, BN-79-1384348-2)
Study type: chronic toxicity
Strain: Daphnia magna
Test concentrations: quadruplicate cultures tested at 5 nominal concentrations: 150, 75, 38, 19, and 9.4micrograms/L. Mean measured concentrations were: 75, 43, 18, 12 and 6 micrograms/L. 20 Daphnia were placed in each aquarium.
Controls: Medium (negative) and positive control
Duration of test material exposure: 21 days
Exposure apparatus: 1.75L glass aquaria charged with stream from proportional diluter
Study endpoint: Survival, fecundity
Observations: dissolved oxygen and temperature daily during the week; hardness, alkalinity, pH, conductance less often. Test material concentrations monitored analytically. Survival checks and offspring production were performed weekdays on study days 7-21.
Results: All Daphnids exposed at 75micrograms/L or greater did not survive beyond 7 days. Offspring production was decreased at 43 micrograms/L for the entire exposure period and at 18 micrograms/L for study days 11, 12 and 13.
Statistical analysis of study data: Yes
MTC: 18-43 micrograms/L
Reliability: Reliable with restrictions
GLP: No
Reference: EG&G Bionomics Aquatic Toxicology Research Laboratory, Report Number BW-79-9-537, The chronic toxicity of S-141 (BN-79-1384348-2) to the water flea (Daphnia magna). Wareham, MA., October, 1979.

III. MAMMALIAN TOXICITY

Test material: 2-ETHYLHEXYL DIPHENYL PHOSPHATE (Lot K-2014)
Study type: Acute mammalian toxicity
Species: Rat
Strain: Not Stated
Sex: Male and female
Number of animals
per dose level: 4 of each sex, weight range 140-300g
Administration: Single dose, oral gavage undiluted
Observations: Body weight prior to dosing and at day 15 post-dose
Pharmacotoxic signs daily through day 15 post-dose
Survival
Results: Acute oral LD50 > 24g/Kg
Statistical analysis of study data: Yes
Reliability: Reliable with restrictions
GLP: Work conducted prior to inception of GLP regulations
Reference: Kettering Laboratory of Applied Physiology Report, "A Comparison of the Toxic Effects of Lot K-2014 Santicizer #141 With That of a Previously Tested Lot", University of Cincinnati, March, 1949, Author, R. A. Kehoe.

Test material: 2-ETHYLHEXYL DIPHENYL PHOSPHATE (Lot K-2014)
Study type: Acute mammalian toxicity
Species: Rat
Strain: Not Stated
Sex: Female and male
Number of animals
per dose level: 12, weight range 152-369g
Number of dose
levels: Two, 5 and 10g/Kg
Administration: Twelve repeated doses - one dose daily for 12 consecutive days, oral gavage undiluted
Observations: Body weight prior to dosing and at day 17
Pharmacotoxic signs daily through day 17
Survival
Results: One animal in each dose group did not survive to the end of the dosing period. Pharmacotoxic signs included soft stools, hair loss and skin irritation around anogenital area (reversible following cessation of dosing). Dose-related weight loss of up to 24%. Weight gain occurred in 21/22 animals following cessation of dosing.
Statistical analysis of study data: Yes
Reliability: Reliable with restrictions

GLP: Work conducted prior to inception of GLP regulations
Reference: Kettering Laboratory of Applied Physiology Report, "A Comparison of the Toxic Effects of Lot K-2014 Santicizer #141 With That of a Previously Tested Lot", University of Cincinnati, March, 1949, Author, R. A. Kehoe.

Test material: 2-ETHYLHEXYL DIPHENYL PHOSPHATE (Lot K-2014)
Study type: Skin irritation, Repeated insult patch test
Species: Human
Strain: Not applicable
Sex: Male and female
Administration: Multiple applications of undiluted test material under nonocclusive dressing and challenge
Observations: Dermal reaction
Results: Not a primary irritant or sensitizer.
Statistical analysis of study data: Yes
Reliability: Reliable with restrictions
GLP: Work conducted prior to inception of GLP regulations
Reference: Industrial Biology Research and Testing Laboratory, Repeated insult patch test with Monsanto Chemical Company – Dytrtol. June, 1959

Test material: 2-ETHYLHEXYL DIPHENYL PHOSPHATE
Study type: Skin irritation
Species: Rabbit (3 animals tested)
Strain: Not stated
Sex: Not stated
Administration: Dermal
Observations: Dermal reaction
Results: Slightly irritating.
Statistical analysis of study data: Not stated
Reliability: Reliable with restrictions
Year: 1971
GLP: Work conducted prior to inception of GLP regulations
Reference: Monsanto Chemical Company Report YO 71-0121

Test material: 2-ETHYLHEXYL DIPHENYL PHOSPHATE
Study type: Eye irritation
Species: Rabbit (3 animals tested)
Strain: Not stated
Sex: Not stated
Administration: Ocular
Observations: Dermal reaction
Results: Slightly irritating.
Statistical analysis of study data: Not stated
Reliability: Reliable with restrictions
Year: 1971

GLP: Work conducted prior to inception of GLP regulations
Reference: Monsanto Chemical Company Report YO 71-0121

Test Material: 2-ETHYLHEXYL DIPHENYL PHOSPHATE (S-141)
Study type: One-generation reproduction study
Test animals: Male and female Sprague-Dawley rats, approx. 7-8 weeks old
Number of test groups; number of animals /group: Control and 3 test groups: 0.2%, 0.4% and 0.8%; 16M and 32F/group
Route of administration: Oral dietary
Study design: Males treated for 70 days prior to mating; females treated for 21 days prior to mating. Pregnant females treated throughout mating, gestation and lactation. Observations: Survival, general appearance, behavior, toxic and pharmacologic effects body weight; food and water consumption, gross necropsy, organs weights (8 organs). Histopathological analysis (10 tissues plus lesions) in high-dose and control animals; pregnancy rate, gestational parameters, litter parameters, pup sex, survival and weight gain.
Results: Two adult animals, a male and a female, did not survive the study. The deaths were judged to be not treatment related. No adverse clinical or behavioral effects were noted for the test animals. Body weight gain in the high-dose group and males of the mid-dose group was suppressed. Food (and water) consumption was statistically-significantly suppressed in high-dose females. Mating indices and reproductive performance were unaffected by treatment. F1 pup body weight gain was reduced in the mid- and high-dose groups; 21-day survival was reduced in the high-dose pup group. A dose-related increase in relative and absolute liver and adrenal weight was seen in each sex of the parental and F1 generation.
NOAEL: The reproductive NOAEL was 0.2% dietary (approx. 144mg/kg/day)
Statistical analysis of study data: Yes
Reliability: Reliable
GLP: Yes
Reference:. BIBRA Report 804(7)/2/920: A single generation reproduction study with 2-ethylhexyl diphenyl phosphate (EHDP) in rats. BIBRA Toxicology International, Surrey, UK, December, 1992

Test Material: 2-ETHYLHEXYL DIPHENYL PHOSPHATE (S-141)
Study type: Repeated dose (Subchronic) toxicity study in rats
Test animals: Male and female Sprague-Dawley rats, approx. 4 weeks old
Number of test groups: number of animals /group: Control and 3 test groups: 0.2%, 0.4% and 0.8%; 10M and 10F/group
Duration of test material treatment: 90 days
Route of administration: Oral dietary
Study design: Animals received test or control diet for 90 days and then sacrificed.
Observations: Survival, general appearance, behavior, toxic and pharmacologic effects

body weight (twice weekly) ; food and water consumption, urinalysis (study days 42 and 90) hematology and clinical chemistry at necropsy, gross necropsy, organs weights (9 organs), histopathological analysis (33 tissues plus lesions) in high-dose and control animals as well as liver, adrenal and ovary tissue from low- and mid-dose animals.

Results: All animals survived the study. No adverse behavioral effects were noted for the test animals. Body weight gain in the high- and mid-dose group and males of the mid-dose group was suppressed, statistically-significantly in the high-dose only. Food (and water) consumption was suppressed in high-dose females leading to signs of dehydration. Hematocrit and hemoglobin were reduced in a dose-related and statistically-significant manner. Other clinical chemistry changes indicate liver, kidney, testes and ovary changes. There was a dose-related, statistically-significant increase in relative and absolute liver weight in both sexes. The liver weight changes were accompanies by histopathologic changes consistent with enzyme induction. All treated animals showed dose-related statistically-significant and increased adrenal weights wich were accompanied by an increase in vacuolated cells of the mid- and high-dose animals. There were changes (increases) in kidney, teste and brain weight but without histopathological findings. High-dose females showed hyperplasia of the interstitial gland cells in ovaries.

NOAEL: The NOAEL was <0.2% dietary (approx. 160mg/kg/day for males and 174mg/kg/day for females)

Statistical analysis of study data: Yes

Reliability: Reliable

GLP: Yes

Reference: BIBRA Report 804/4/90: A 90-day feeding study with 2-ethylhexyl diphenyl phosphate (EHDP) in rats. BIBRA Toxicology International, Surrey, UK, January, 1990

IV. GENETIC TOXICITY

Test Material: 2-ETHYLHEXYL DIPHENYL PHOSPHATE (S-141)
Lot QH-11411 BO 78-80

Study type: Microbial cell mutation assay

Testor strains: Salmonella typhimurium TA-1535, TA-1537, TA-1538, TA-98, TA-100
Saccharomyces cerevisiae D4

Number of concentrations tested: 5 plus solvent and positive controls (6 positive control compounds)

Exogenous metabolic activation: Arochlor-induced rat liver microsome S-9

Route of administration: Plate incorporation assay

Cytotoxicity evaluation: Cell growth evaluated (qualitatively)

Study endpoint: Auxotrophic cell mutation

Results: Negative for mutagenicity with and without metabolic activation.

Statistical analysis of study data: No
Reliability: Reliable
GLP: No, but data quality reviewed by contractor and study records (protocol, SOP's staff training, study raw data) maintained
Reference:. Litton Bionetics, Inc., Mutagenicity evaluation of S-141 in the Ames salmonella/microsome plate test. Kensington, Md., June, 1978

Test Material: 2-ETHYLHEXYL DIPHENYL PHOSPHATE (S-141)
Lot QH-11411 BO 78-84
Study type: Mammalian cell mutation assay
Testor strains: Fischer mouse lymphoma L5178Y line
Number of concentrations tested: 5 plus solvent (DMSO) and
positive controls (EMS and DMN)
Testing in duplicate cultures
Exogenous metabolic activiation: Arochlor-induced rat liver microsome S-9
Route of administration: Plate incorporation assay
Observations: Cell growth (percent), total viable colonies, total mutant colonies, relative cloning efficiency
Study endpoint: Specific locus forward cell mutation at the thymidine kinase locus
Results: Negative for mutagenicity with and without metabolic activation.
Statistical analysis of study data: No
Reliability: Reliable
GLP: No, but data quality reviewed by contractor and study records (protocol, SOP's staff training, study raw data) maintained
Reference:. Litton Bionetics, Inc., Mutagenicity evaluation of S-141 in the mouse lymphoma forward mutation assay. Kensington, Md., August, 1978

Test Material: 2-ETHYLHEXYL DIPHENYL PHOSPHATE (S-141)
Study type: In vivo bone marrow chromosome study in rats
Test animals: Male and female Sprague-Dawley rats, approx. 50 days old
Number of test groups; number of animals /group: 3 test groups: 15,000 mg/kg, 5,000 mg/kg and 1,500 mg/kg; 24M and 24F/group
Number of control groups; number of animals/group: Vehicle (corn oil) 24M and 24F/group; positive control (cyclophosphamide) 24M and 24F/group
Duration of test material treatment: Single treatment
Route of administration: Oral gavage
Sacrifice times: 6, 12, 24 and 48 hours post-dosing
Study endpoint: Structural and numerical aberrations in bone marrow cell chromosomes
Observations: Survival, general appearance, behavior, toxic and pharmacologic effects (twice daily); Body weight at initiation and sacrifices;
Number of metaphase spreads evaluated per animal: 5 animals examined per group; 60metaphase spreads/animal per group

Results: Test animals at each does level lost weight in a statistically-significant, dose-related manner following dosing . Four mid-dose animals died on study. No statistically-significant differences in chromosome structural defects or number between treated and control animals

Statistical analysis of study data: Yes

Reliability: Reliable

GLP: Yes

Reference:. Hazleton Laboratories America, In vivo bone marrow chromosome study ib rats, HLA Report HL-83-209, Vienna, Va., November, 1983